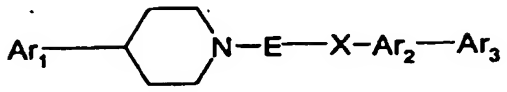
Claims

1. A compound of formula (I), physiologically acceptable prodrugs, salts or solvates thereof;



(I)

wherein

Ar_1 is:

(i) phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl; or

(ii) heterocyclyl selected from the list consisting of: monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be independently saturated, partially unsaturated or aromatic, provided that at least one ring is aromatic;

where Ar_1 is optionally substituted by 1-4 R^1 groups which may be the same or different;

Ar_2 is a phenyl group, a 5-6 membered heteroaromatic group or a bicyclic heteroaromatic group, each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, C_{1-6}acyl, C_{1-6}acyloxy, amino, C_{1-4}alkylamino, di-C_{1-4}alkylamino, $-(CH_2)_nOH$, $-(CH_2)_nNR_xR_y$, $-O(CH_2)_nO(CH_2)_mOR^a$, $-O(CH_2)_nC(O)NR_xR_y$, $-O(CH_2)_nCN$, C_{2-5}alkenyl, $-O(CH_2)_nCO_2R^a$, $-OSO_2(CH_2)_pCH_3$, $-OSO_2NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is:

(i) phenyl, naphthyl or phenyl fused by a C_{3-8}cycloalkyl; or

(ii) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5-14 ring atoms, wherein said radicals contain a total of from 1-4 ring heteroatoms independently selected from oxygen, nitrogen and sulfur, and wherein individual rings of said radicals may be

independently saturated, partially unsaturated, or aromatic, providing that at least one ring is aromatic,

wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: hydroxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkenyloxy, C_{1-4}perfluoroalkoxy, C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, nitro, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, C_{1-4}alkoxycarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl, di-C_{1-4}alkylaminocarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylaminosulfonyl, di-C_{1-4}alkylaminosulfonyl, C_{1-4}alkylsulfonyl and C_{1-4}alkylsulfoxy;

E is n-butylene;

X is $-CONR^a-$ or $-NR^aCO-$ (where the left hand side of the linkage is attached to E);

wherein

R^1 is halogen, C_{1-4}alkoxy or C_{1-4}alkyl;

R^a is C_{1-4}alkyl or hydrogen;

R_x and R_y are independently hydrogen, C_{1-4}alkyl, hydroxy or C_{1-4}alkoxy, where R_x and R_y are not both hydroxy or both C_{1-4}alkoxy; or R_x and R_y together with the nitrogen to which they are attached form a 5-membered ring which ring is optionally substited by $-O(CH_2)_nC(O)NR_xR_y$, $-O(CH_2)_nCN$, $-O(CH_2)_nO(CH_2)_mOR^a$, $-O(CH_2)_nCO_2R^a$, $-OSO_2NR_xR_y$, $-OSO_2(CH_2)_pCH_3$, $-(CH_2)_nC(O)NR_xR_y$, $-(CH_2)_nCN$, $-(CH_2)_nO(CH_2)_mOR^a$, $-(CH_2)_nCO_2R^a$, $-(CH_2)_nC(O)R^a$, $-SO_2NR_xR_y$, $-SO_2(CH_2)_pCH_3$, $-CH=CHC(O)NR_xR_y$, $-CH=CHCN$, $-CH=CHCO_2R^a$, $-CO_2R^a$, $-C(O)R^a$, $-C(O)NR_xR_y$ and C_{2-5}alkenyl;

n and m are independently 1-4; and

p is 0-4.

2. A compound according to claim 1 wherein Ar_1 is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl.

3. A compound according to claim 2 wherein Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl.

4. A compound according to any preceding claim wherein X is $-NR^aCO-$.

5. A compound according to any preceding claim wherein Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl.

6. A compound according to claim 5 wherein Ar_2 is optionally substituted by one or two substituents independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ (where R_x and R_y are independently hydrogen or C_{1-4}alkyl and n is 1-3) or $-CO_2(CH_2)_pCH_3$ (where p is 0-3).

7. compound according to any preceding claim wherein Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl.

8. A compound according to claim 7 wherein Ar_3 is substituted by C_{1-4}alkylsulfonylamino, fluoroC_{1-4}alkylsulfonylamino, C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen, nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl or di-C_{1-4}alkylaminocarbonyl.

9. A compound according to claim 1 wherein

Ar_1 is phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, indolyl, benzofuranyl, benzothiophenyl or indazolyl; where Ar_1 is optionally substituted by 1-4 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile,

C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is $-NR^aCO-$;

R^1 is halogen, C_{1-4}alkoxy or C_{1-4}alkyl;

R^a is C_{1-4}alkyl or hydrogen;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

10. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

11. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: hydroxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

12. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is pyridyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

13. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, aminoC_{1-4}alkyl, mono-C_{1-4}alkylaminoC_{1-4}alkyl, di-C_{1-4}alkylaminoC_{1-4}alkyl, $-O(CH_2)_nC(O)NR_xR_y$ and $-CO_2(CH_2)_pCH_3$;

Ar_3 is phenyl, pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar_3 is optionally substituted by 1-4 groups independently selected from the group consisting of: C_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_3$, $-NHSO_2CH(CH_3)_2$), fluoroC_{1-4}alkylsulfonylamino (such as $-NHSO_2CH_2CF_3$), C_{1-4}alkylcarbonylamino, fluoroC_{1-4}alkylcarbonylamino, halogen (such as chlorine), nitrile, C_{1-4}perfluoroalkyl, C_{1-4}alkylcarbonyl, fluoroC_{1-4}alkylcarbonyl, aminocarbonyl, C_{1-4}alkylaminocarbonyl and di-C_{1-4}alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C_{1-4}alkoxy or C_{1-4}alkyl;

R_x and R_y are independently hydrogen or C_{1-4}alkyl;

n is 1-3; and

p is 0-3.

14. A compound according to claim 1 wherein

Ar_1 is phenyl, 1,2,3,4-tetrahydronaphthyl or indolyl; where Ar_1 is optionally substituted by 1-2 R^1 groups which may be the same or different;

Ar_2 is phenyl, pyridyl, thiazolyl, oxazolyl, pyrazolyl or imidazolyl; each of which is optionally substituted by 1-4 groups independently selected from the list: C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl,

aminoC$_{1-4}$alkyl, mono-C$_{1-4}$alkylaminoC$_{1-4}$alkyl, di-C$_{1-4}$alkylaminoC$_{1-4}$alkyl, -O(CH$_2$)$_n$C(O)NR$_x$R$_y$ and -CO$_2$(CH$_2$)$_p$CH$_3$;

Ar$_3$ is pyridyl, pyridazinyl, pyrimidinyl, furyl or thienyl; wherein Ar$_3$ is optionally substituted by 1-4 groups independently selected from the group consisting of: C$_{1-4}$alkylsulfonylamino (such as -NHSO$_2$CH$_3$, -NHSO$_2$CH(CH$_3$)$_2$), fluoroC$_{1-4}$alkylsulfonylamino (such as -NHSO$_2$CH$_2$CF$_3$), C$_{1-4}$alkylcarbonylamino, fluoroC$_{1-4}$alkylcarbonylamino, C$_{1-4}$alkylcarbonyl, fluoroC$_{1-4}$alkylcarbonyl, aminocarbonyl, C$_{1-4}$alkylaminocarbonyl and di-C$_{1-4}$alkylaminocarbonyl;

E is n-butylene;

X is –NHCO-;

R^1 is C$_{1-4}$alkoxy or C$_{1-4}$alkyl;

R$_x$ and R$_y$ are independently hydrogen or C$_{1-4}$alkyl;

n is 1-3; and

p is 0-3.

15. A compound according to claim 1 selected from the list:

2-Hydroxymethyl-4'-trifluoromethyl-biphenyl-4-carboxylic acid {4-[4-(1H-indol-3-yl)-piperidin-1-yl]-butyl}-amide (Example 1);

2-(4-Cyano-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 7);

2-(4-Chloro-phenyl)-4-hydroxymethyl-thiazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 10);

5-(4-Cyano-phenyl)-2-(2-hydroxy-ethyl)-2H-pyrazole-3-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 21);

4-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 23);

4-(5-Chloro-pyridin-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 32);

4-(6-Chloro-pyridin-3-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-benzamide (Example 34);

6-(4-Chloro-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 38);

6-(4-Cyano-phenyl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 39);

6-(5-Chloro-thiophen-2-yl)-N-{4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-nicotinamide (Example 40); and

2-(4-chlorophenyl)-1,4-dimethyl-1H-imidazole-5-carboxylic acid {4-[4-(1-methoxy-5,6,7,8-tetrahydro-naphthalen-2-yl)-piperidin-1-yl]-butyl}-amide (Example 45).

16. A pharmaceutical composition comprising a compound as defined in any preceding claim and a pharmaceutically acceptable carrier or diluent.

17. The use of a compound defined in any one of claims 1 to 15 in the manufacture of a medicament for use in the treatment of conditions resulting from elevated circulating levels of LDL-cholesterol.

18. A compound defined in any one of claims 1 to 15 for use as a medicament.